A FACILE, MECHANOCHEMICAL, SOLVENT AND CATALYST-FREE SYNTHESIS OF FUNCTIONALIZED 4-THIAZOLIDINONES

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Abstract:
A highly eco-friendly greener approach based on the mechanochemical method using mortar and pestle is explored for the preparation of a variety of functionalized 4-thiazolidinones. The developed methodology does not require the use of harmful or expensive reagents and organic solvents and requires very less reaction time with easy isolation. The explored greener approach for the synthesis of 4-thiazolidinones is an important in terms of their usefulness for their valuable pharmacological properties.

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A FACILE, MECHANOCHEMICAL, SOLVENT AND CATALYST-FREE SYNTHESIS OF FUNCTIONALIZED 4-THIAZOLIDINONES

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A highly eco-friendly greener approach based on the mechanochemical method using mortar and pestle is explored for the preparation of a variety of functionalized 4-thiazolidinones. The developed methodology does not require the use of harmful or expensive reagents and organic solvents and requires very less reaction time with easy isolation. The explored greener approach for the synthesis of 4-thiazolidinones is an important in terms of their usefulness for their valuable pharmacological properties.

Key words: Mechanochemistry, green chemistry, grinding, 4-thiazolidinones, solvent-free synthesis.

One of the main challenges for the medicinal chemistry is to develop the useful therapeutic agents for the treatment of various type of infections against increasing multi-drug resistant microbial pathogens as well as applications against different disorders. In literature, there are numerous small membered biologically active molecules which has drug like properties. Of these, five membered rings, containing two heteroatoms such as 4-thiazolidinone ring have been observed in core structure in various biologically active molecules.¹-⁴ The immense importance of 4-thiazolidinones based scaffolds in various medications including anti-tubercular, anti-cancer, anti-diabetic, anti-microbial, anti-inflammatory, anti-malarial, antiviral, aesthetic etc. has fascinated organic chemists for their synthesis via newer synthetic methods⁵-⁸.

The conventional methods for the preparation of 4-thiazolidinones involves the high temperature conditions, use of organic solvents, expensive catalysts, use of column for the separation and purification process⁹,¹⁰. The impact of global warming and interest towards the decrease in usage of harmful chemicals have encouraged researchers to revisit and further developing simple, economical and environment friendly pathways for the synthesis of 4-thiazolidinone moiety.

Figure 1. Functionalized 4-thiazolidinones based FDA approved drugs.

Keeping in mind, the biological activities of 4-thiazolidinones,¹¹⁻¹⁴(Figure 1) and realizing the importance of the green methodologies in organic synthesis, it was thought worthwhile to explore the greener methods for the preparations of functionalized 4-thiazolidinones.

Figure-2 Earlier method for the formation of functionalized 4-thiazolidinones
On the other hand, mechanochemical synthesis is emerging as a new green approach for the preparation of various heterocycles via C-O, C-N, C-S bond formation through methods like grinding, sonication\textsuperscript{11-18}. The simple economical method offers several benefits such as less use of harmful toxic solvents, use of eco-friendly chemicals, less usage of toxic and expensive metal-based catalyst, lesser release of harmful wastes and no or negligible by-product formation\textsuperscript{19,21}. Since the reaction does not result in the formation of any by-product, the yield of the reaction is also remarkably higher as compared to conventional methods employed.

Keeping in view of the diverse pharmacological profile of functionalized 4-thiazolidinones and the upsurge in their synthetic developments,\textsuperscript{22-27} we have explored the facile and greener approach for the synthesis of functionalized thiazolidin-4-ones. The current methodology involved the simple grinding method using mortar and pestle. The developed methodology did not involve the use of any expensive catalyst, solvent or high temperature conditions and the reaction completed within few minutes. Moreover, the reaction did not result in the formation of any by-product and afforded a variety of 4-thiazolidinone derivatives 1a-k in high yield.

2. Results and discussion

The starting material were procured commercially. The variety of functionalized amines and aldehyde were explored in the initial synthesis of the functionalized imines by traditional methods.\textsuperscript{28} The functionalized imines 4a-j were explored in the synthesis of functionalized thiazolidin-4-ones. The optimizations of employed methodology were performed based upon the achieving the better desired product yields as well as time required for the completion of the reactions with variation in reaction conditions on the basis of amount of thioglycolic acid and anhydrous sodium sulphate (dehydrating agent). The investigated reaction model obtained after optimization of model reaction for the synthesis of 2-(2-nitrophenyl)-3-phenylthiazolidin-4-one is represented in Table 1. It is evident that without the use of dehydrating agent the reaction was quite slow and resulted in poor yield (Table 1, entry 1). Further, addition of sodium sulphate into the reaction mixture during grinding not only the uplifted but also, enhanced the product yield (Table 1, entry 2). It is evident that on further grinding the product yield was found to be marginally improved (Table 1, entry 3). Increasing the amount of thioglycolic acid and dehydrating agent maximum product yield was reported (Table 1, entry 4). At last, (Table 1, entry 5), grinding time-period was recorded and maximum product yield of 95% was obtained after 12 min of grinding.

Table 1 Optimization of the reaction condition for the synthesis of functionalized thiazolidin-4-ones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine (eq.)</th>
<th>Thioglycolic acid (eq.)</th>
<th>Dehydrating agent</th>
<th>Time (Min.)</th>
<th>Yield* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>1.0</td>
<td>.</td>
<td>15</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>1.0</td>
<td>NaSO\textsubscript{4} \textsuperscript{1} (1 eq.)</td>
<td>15</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>1.2</td>
<td>NaSO\textsubscript{4} \textsuperscript{1} (1 eq.)</td>
<td>5</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>1.0</td>
<td>NaSO\textsubscript{4} \textsuperscript{1} (2 eq.)</td>
<td>8</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>1.0</td>
<td>1.2</td>
<td>NaSO\textsubscript{4} \textsuperscript{1} (2 eq.)</td>
<td>8</td>
<td>95</td>
</tr>
</tbody>
</table>

*Isolated yields.

Scheme 1. Synthesis of 2,3-diphenyl substituted thiazolidin-4-ones.

After optimizing the reaction conditions, a variety of arylaldehyde 3 and amines 2 were tested to yield a series of substituted imines 4 which on condensation reaction with thioglycolic acid (1.5 eq.), sodium sulphate (2.0 eq.) using traditional grinding method using mortar and pestle for 8 minutes afforded 4-thiazolidinone derivatives 1a-k in high yield (Scheme 1). A wide range of electron-withdrawing and electron-donating 2,3-diphenyl substituted thiazolidin-4-one derivatives were obtained in good yield (Table 2, entries 1-11). However, in case of glyoxal desired thiazolidin-4-one derivatives was not obtained probably due to steric crowding because of the presence of two thiazolidine-4-one rings (bisthiazolidin-4-ones).
In conclusion, the current manuscript describes the facile solvent free and green mechanochemical approach for the synthesis of functionalized thiazolidin-4-ones. The employed green approach has broader substrate scope and afforded in good yields of thiazolidin-4-ones in comparatively short reaction time with easy isolation. The current approach is also an important in terms of the diverse pharmacological profile of functionalized thiazolidin-4-ones.

References
2. Chawla, PA; Wahan, SK; Negi, M; Faruk, A; Chawla, V. Journal of Heterocyclic Chemistry, 2022.

### Table 2. Substrate scope in the synthesis of 2,3-diphenyl substituted thiazolidin-4-ones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R′</th>
<th>R″</th>
<th>Product (1)</th>
<th>Time (Min.)</th>
<th>Yield (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C6H5</td>
<td>C6H5</td>
<td>1a</td>
<td>8</td>
<td>90 (4.93 g)</td>
</tr>
<tr>
<td>2</td>
<td>C6H5</td>
<td>2-NO2 C6H4</td>
<td>1b</td>
<td>8</td>
<td>95 (6.12 g)</td>
</tr>
<tr>
<td>3</td>
<td>4-Cl C6H4</td>
<td>C6H5</td>
<td>1c</td>
<td>8</td>
<td>94 (4.26 g)</td>
</tr>
<tr>
<td>4</td>
<td>4-CH3 C6H4</td>
<td>C6H5</td>
<td>1d</td>
<td>8</td>
<td>82 (4.12 g)</td>
</tr>
<tr>
<td>5</td>
<td>2-CH3 C6H4</td>
<td>C6H5</td>
<td>1e</td>
<td>8</td>
<td>90 (4.52 g)</td>
</tr>
<tr>
<td>6</td>
<td>2-CH3 C6H4</td>
<td>2-NO2 C6H4</td>
<td>1f</td>
<td>8</td>
<td>95 (5.57 g)</td>
</tr>
<tr>
<td>7</td>
<td>4-F C6H4</td>
<td>C6H5</td>
<td>1g</td>
<td>8</td>
<td>90 (4.42 g)</td>
</tr>
<tr>
<td>8</td>
<td>C6H5</td>
<td>4-NO2 C6H4</td>
<td>1h</td>
<td>8</td>
<td>92 (5.93 g)</td>
</tr>
<tr>
<td>9</td>
<td>C6H4 (cyclohexyl)</td>
<td>C6H5</td>
<td>1i</td>
<td>8</td>
<td>90 (4.73 g)</td>
</tr>
<tr>
<td>10</td>
<td>C6H5</td>
<td>C6H4(benzyl)</td>
<td>1j</td>
<td>8</td>
<td>85 (4.27 g)</td>
</tr>
<tr>
<td>11</td>
<td>C6H4(butyl)</td>
<td>C6H5</td>
<td>1k</td>
<td>8</td>
<td>95 (6.11 g)</td>
</tr>
<tr>
<td>12</td>
<td>C6H5</td>
<td>CHO</td>
<td>-</td>
<td>8</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

bOptimized reaction conditions: imine (1.0 eq.), thioglycolic acid (1.5 eq.), Na2S03 (2 eq.). No solvent, grinding (9-12 min); bIsolated percentage yield and mass yield.

The imines derived from aliphatic amine afforded better yield of thiazolidin-4-ones 1a-k (Table 2; Entries 9-11). However, the imines with aryl substituents afforded slightly low yield of thiazolidin-4-ones 1 (Table 2; Entries 1-8). However, the formation of thiazolidin-4-ones 1 did not occur using glyoxaldehyde as aldehyde counterpart of imine (Table 2; Entries 12). All the prepared 2,3-diphenyl substituted thiazolidin-4-ones 1a-k were characterized with the help of spectroscopic evidences. The 1H NMR of all prepared thiazolidin-4-ones 1a-k were confirmed by the presence of singlet peak of CH bonded to substituted phenyl ring at range of 6.14-6.44 and a doublet due to methylene hydrogens at 3.80-4.00. The probable mechanism for the solvent-free synthesis of 2,3-diphenyl substituted thiazolidin-4-one derivatives in illustrated in Scheme 2. The mechanism involved initial attack of nucleophilic nitrogen of amines to electrophilic carbonyl carbon of benzaldehydes with the release of water molecule and formation of double bond. Further, nucleophilic sulphur of thioglycolic acid attacks iminic carbon with the shifting of electrons followed by attack of nucleophilic nitrogen on carbonylic carbon resulting in the formation of thiazolidine ring with release of water molecule. Hence, the use of anhydrous sodium sulphate as mediator in the reaction absorbs the released water molecules thereby enhances and shifts the reaction in the forward direction.
for some time, solid precipitates were found at the diethyl ether and hexane in the ration 3:1 dropwise impure product was purified by adding the mixture of filtered and dried to collect the crude product. The product obtained was dried using magnesium sulphate, was done by using ethyl acetate (2*20 mL). the crude found to be completed, the work-up of the reaction was monitored by using tlc. After the reaction was 12 mins till the completion of reaction. The reaction thioglycolic acid mixed and grinded using mortar and pestle with the mixture of prepared series of imines sulphate (2 eq.) as dehydrating agent. After isolation, solvent at room temperature in the presence of sodium benzaldehydes aromatic amines 4(a-k) reaction involved the preparation of series of imines substituted thiazolidin-4-one derivatives 1(a-k).

General procedure for the synthesis of 2,3-diphenyl substituted thiazolidin-4-one derivatives 1(a-k). The reaction involved the preparation of series of imines 4(a-k) by stirring the mixture of various aliphatic and aromatic amines 1 (1 eq.) and various substituted benzaldehydes 2(a-k) (1.1 eq.) in dichloromethane as solvent at room temperature in the presence of sodium sulphate (2 eq.) as dehydrating agent. After isolation, the mixture of prepared series of imines 4(a-k) were mixed and grinded using mortar and pestle with thioglycolic acid 5 (1.5 eq.) and NaSO₄ (2 eq.) for 9-12 mins till the completion of reaction. The reaction was monitored by using tlc. After the reaction was found to be completed, the work-up of the reaction was done by using ethyl acetate (2*20 mL). the crude product obtained was dried using magnesium sulphate, filtered and dried to collect the crude product. The impure product was purified by adding the mixture of diethyl ether and hexane in the ration 3:1 dropwise with stirring. After, keeping the reaction mixture aside for some time, solid precipitates were found at the bottom of the beaker. Mother liquor was decanted off and the product obtained was dried to obtain pure solid compounds of 2,3-diphenyl substituted thiazolidin-4-one derivatives. The same process was repeated 2-3 times to obtain product without any impurities.

29. 2,3-diphenylthiazolidin-4-one (1a): Yield 90%; yellow solid, mp.: 127-129°C; IR(KBr) cm⁻¹ : 1655 (C=O), 1H NMR (500 MHz, DMSO): 3.98 (dd, 2H, CH); 7.31 (dd, 1H, CH); 7.57 (dd, 1H, CH); 7.72 (dd, 2H, CH); 7.9 (d, 2H, CH); 8.0 (dd, 2H, CH) ppm.

30. 2-(2-nitrophenyl)-3-phenylthiazolidin-4-one (1b): Yield 95 %; pale yellow solid, mp.: 136°C; IR(KBr) cm⁻¹ : 1654 (C=O), 1595-1313 (NO₂); 1H NMR (500 MHz, DMSO): 6.44 (s, 1H, CH); 7.31 (dd, 1H, CH); 7.54 (d, 1H, CH); 7.72 (dd, 1H, CH); 7.9 (d, 2H, CH); 8.0 (dd, 2H, CH) ppm.


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Conflict of Interest
No potential conflict of interest.
Mechanochemical solvent-free synthesis of 4-thiazolidinones derivatives

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Supporting Information

**Procedure:** The synthesis of 2,3-diphenyl substituted thiazolidin-4-one derivatives 1(a-k). The reaction involved the preparation of series of imines 4(a-k) by stirring the mixture of various aliphatic and aromatic amines 2 (1 eq.) and various substituted benzaldehydes 3(a-k) (1.1 eq.) in ethanol as solvent at room temperature in the presence of sodium sulphate (2 eq.) as dehydrating agent. Further, the mixture of prepared series of imines 4(a-k) were crushed and grinded using mortar and pestle with thioglycolic acid 5 (1.5 eq.) and Na$_2$SO$_4$ (2 eq.) for 9-12 mins till the completion of reaction. The reaction was monitored by using tlc. After the reaction was found to be completed, the work-up of the reaction was done by using ethyl acetate (2*20 mL). The crude product obtained was dried using magnesium sulphate, filtered and dried to collect the crude product. The impure product was purified by adding the mixture of diethyl ether and hexane in the ration 3:1 dropwise with stirring. After, keeping the reaction mixture aside for some time, solid precipitates were found at the bottom of the beaker. Mother liquor was decanted off and the product obtained was dried to obtain pure solid compounds of 2,3-diphenyl substituted thiazolidin-4-one derivatives. The same process was repeated 2-3 times to obtain product without any impurities.

![Fig. S1 Synthesis of diphenyl substituted thiazolidin-4-one derivatives](image)

**Experimental data:**

*2,3-diphenylthiazolidin-4-one (1a):* Yield 90%; yellow solid, mp.- 127-129°C; $^1$H NMR (500 MHz, DMSO); 3.98 (dd, 2H, CH$_2$); 5.84 (s, 1H, CH); 7.31 (dd, 1H, CH); 7.5 (dd, 1H, CH); 7.8 (dd, 2H, CH); 7.9 (d, 2H, CH); 8.0 (dd, 2H, CH) ppm.
2-(2-nitrophenyl)-3-phenylthiazolidin-4-one (1b): Yield 95%; yellow solid, mp. - 189 °C; \(^1\)H NMR (300 MHz, DMSO); 3.92 (dd, 2H, CH); 6.81 (s, 1H, CH); 7.16 (d, 2H, CH); 7.32 (dd, 2H, CH); 7.47 (dd, H, CH); 7.56 (d, H, CH); 7.68 (dd, H, CH), 8.10 (dd, H, CH), 8.13 (dd, H, CH) ppm.

2-phenyl-3-(p-tolyl)thiazolidin-4-one (1d): Yield 82%; yellow brown solid, mp. -115-116°C; \(^1\)H NMR (500 MHz, DMSO); 3.91 (dd, 2H, CH); 6.08 (s, 1H, CH); 2.27 (s, 3H, CH); 7.07 (dd, 1H, CH); 7.05 (dd, 1H, CH); 7.11 (dd, 2H, CH); 7.31 (d, 2H, CH); 7.33 (dd, 2H, CH) ppm.

2-(4-nitrophenyl)-3-phenylthiazolidin-4-one (1h): Yield 92%; yellow solid, mp. - 210 °C; \(^1\)H NMR (400 MHz, DMSO); 3.91 (dd, 2H, CH); 6.08 (s, 1H, CH); 7.63 (dd, 1H, CH); 8.11 (dd, 1H, CH); 8.13 (dd, 2H, CH); 8.17 (d, 2H, CH); 8.37 (dd, 2H, CH) ppm.

Fig. S4 Proton NMR spectra of 1a
Fig. S5 Proton NMR spectra of 1b
Fig. S2 Proton NMR spectra of 1d

Fig. S3 Proton NMR spectra of 1h